THINK LIKE A WORM: VALUE-BASED DECISION MAKING IN *CAENORHABDITIS ELEGANS*

by

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A THESIS

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Approved: _____

Shawn R. Lockery, PhD

Nearly all of our actions are based on making choices. The alternatives and their consequences, with input from our memory, our senses, and other factors, are weighed through an incredibly complex neural process. However, this process remains poorly understood. Using a simple food-choice behavioral assay, we tested the decision-making of *Caenorhabditis elegans*, a nematode worm. It is hoped that a clear understanding, both at the neural level and at the behavioral level, of the decision-making process of this organism will help elucidate analogous processes in higher organisms such as humans.

We found that *C. elegans,* when presented with food sources of equal concentration but variable perceived danger, showed a higher tolerance for danger when the food concentration was low. Additionally, when presented with a variety of food choices, equally spaced along a gradient of decreasing food concentration and perceived danger, we found that the animals make highly rational, value-based decisions.

The results presented in this thesis suggest that *C. elegans* is a useful organism with which to study choices, because of its capacity for rational, value-based decision making.

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Table of Contents

Background

Almost all of our actions from day to day involve making decisions. Whether we are deciding what to have for breakfast, whether to bike or walk someplace, or what music to listen to, we are weighing two or even several possible choices and their consequences. In dangerous or resource-poor situations, the gravity of the choices becomes still clearer. Decision making is an incredibly complex process on the neural level, engaging many regions of the brain and utilizing input from all of our senses.

However, this process remains poorly understood. Discovering and clarifying some of the underlying mechanisms, pathways, and regulators behind our behavior can help reveal some of what is unknown about the neural process. This will allow for further advances in neuroscience, which have the potential to impact such fields as psychology, ethics, and economics, in addition to informing our daily life.

Decision making varies in complexity at the behavioral level, and can be broadly categorized into behavioral choice and value-based decision making (1). Behavioral choice refers to the selection of one of a set of mutually-exclusive alternatives based on the low-level neural computation of input from various stimuli (2), whereas value-based decisions are reached through higher-order calculations of the benefits and drawbacks of each choice, wherein the subject is attempting to maximize satisfaction of the subject's preferences.

Choosing a model organism

In order to efficiently and accurately study the mechanisms of decision making, a model organism with certain favorable characteristics is needed. Primates, such as humans and monkeys, are difficult to work with, are incredibly complex, and cannot

usually be manipulated at the neurophysiological level, which limits the scope of discovery (1). On the other hand, *Caenorhabditis elegans*, a nematode worm roughly 1 mm in length that subsists on bacteria found in rotting fruits, possesses a set of characteristics that make it an advantageous tool for studying decision making behavior (3, 4). *C. elegans* is a much simpler animal than any primate, containing only 302 neurons to our 86 billion (4). The animal has been the subject of intense study for decades, and some results have been compiled to produce an almost complete wiring diagram—essentially a complete map of the connections within the nervous system (1, 5). This diagram makes synapse-level pathway manipulation and determination possible. Additionally, *C. elegans* is conducive to genetic manipulation, because of regular development across individuals, short generation time, large number of progeny per generation, ease of maintenance, and other factors (1, 3, 6). The animals are also transparent, which allows for simplified *in vivo* visualization. Several techniques, such as calcium imaging and fluorescent labeling, have been developed and adapted for this species (3).

There is substantial genetic overlap between *C. elegans* and humans. At least 38% of protein-coding genes within the *C. elegans* genome have orthologs within the human genome, over 60% of human genes have a *C. elegans* ortholog, and a full 40% of genes implicated in human diseases can also be found in similar form in *C. elegans* (3). The two organisms also use similar sets of neurotransmitters and hormones, and their respective receptors also largely overlap (1, 7, 8). These similarities allow for easier application of findings in this organism to human neuroscience and medicine.

Caenorhabditis elegans

The lifecycle of *C. elegans* consists of an embryonic stage, 4 larval stages, and a fertile adult stage (Figure 1). By the fourth stage of larval development, L4, sex can be determined through microscopy. Roughly 1% of worms are male, and the rest are hermaphrodites (3). Each hermaphrodite possesses 302 neurons—males have 383—which are capable of controlling stimulus reception and motor response for the entire animal (3). Each animal contains 2 amphids, which are the primary chemosensory organs (4, 6). These organs, situated near the head and each containing 12 neurons, are capable of olfaction, taste, thermosensation, and mechanosensation (6). The animals' behavior—the coordinated response to internal and external stimuli—can be broadly placed into 3 categories: housekeeping, escape behavior, and habitat and resource localization (1).

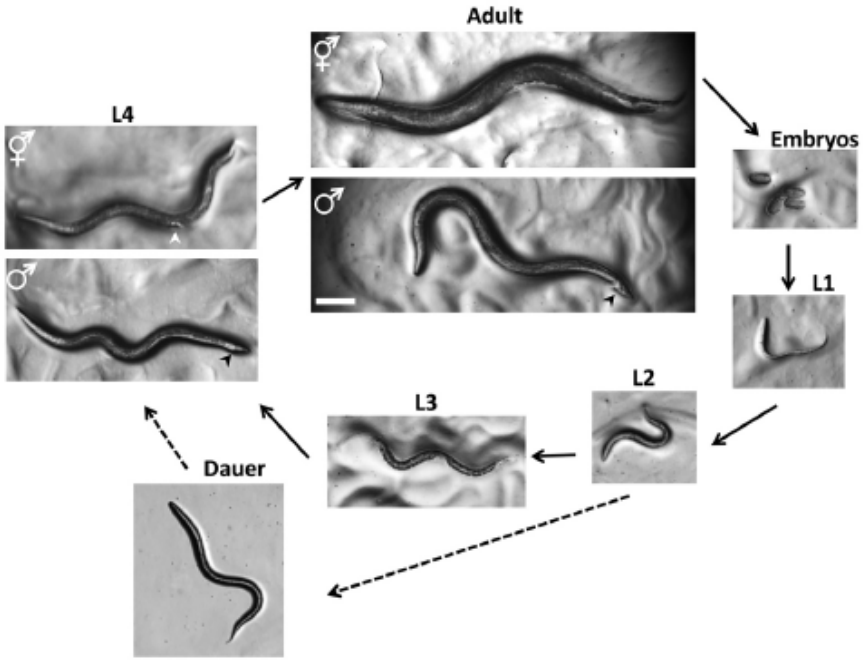

Figure 1. Lifecycle of *Caenorhabditis elegans* (3).

At 20°C, embryos progress to larval stage 1 (L1) by about 16 h. The 4 larval stages, characterized by small developmental changes, last roughly 16 h for L1 and 12 h each for L2-L4. About 12 h into the adult stage, worms begin producing progeny, which continues for 2-3 days in hermaphrodites. Male worms greatly complicate population genetics, and are therefore excluded in most studies. The dauer life stage, connected by dotted arrows, is selected under starving conditions; dauer worms are unable to eat, arresting development, and can survive for months while they search for a food source.

Housekeeping behaviors include regular fixed action patterns such as feeding and reproduction. Escape behavior is rapid reflex movement in response to threatening stimuli such as touch and heat. Habitat and resource location, the most diverse category to study, includes the relatively complicated neural processing required to move toward sources of positive stimuli and away from sources of negative stimuli (1). This category uses processes such as chemotaxis, the motion up or down a chemical gradient, and thermotaxis, the motion up or down a thermal gradient (1). With these

processes, individuals can detect food sources, dangers, and other environmental factors, which forms the foundation for my project.

Value-based decision making processes in *C. elegans*

Value-based decision making can be difficult to distinguish from simpler behavioral choice. The key characteristic is the neurological calculation of maximizing satisfaction. The calculation involves the relative value, to the subject, of all the alternatives. To illustrate, a simple example is shown in Figure 2. In this example, there is a budget of $10 to buy a snack. Two products are available: a small bag of chips for $1, and a piece of candy for $2. Assuming a stipulation that the entire budget be spent, there are exactly 6 alternatives available, as listed in the figure. There is a distinct trade-off in effect: starting with a full 10 bags of chips, every exchange for a candy results in a deduction of 2 bags of chips.

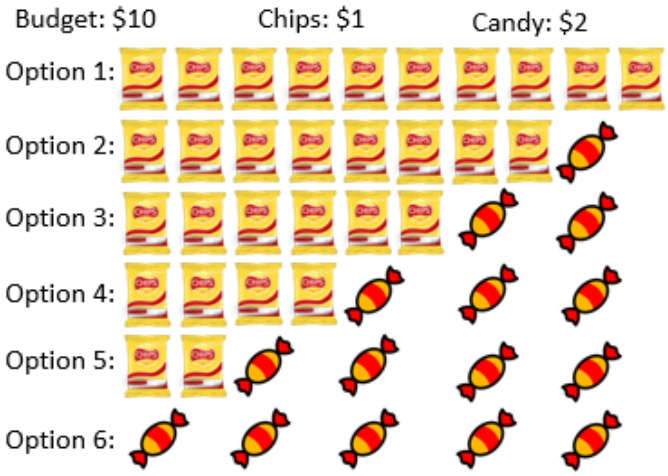

Figure 2. Simplistic schematic of value-based decision making.

In this example, a person could choose any of the 6 possibilities, depending on personal preference for the two items. Common choices might be options 3 and 4, because they represent the most even distributions of the budget between the products. The set of 6 options is referred to as a menu, a choice set, or a budget line. One could imagine another budget line with $12 available, and therefore all different choices.

Analogous experiments have been devised to probe value-based decision making in *C. elegans*. One such experiment, as in the illustrative example (Figure 2), presents two alternative food types. In this experiment, two different bacterial strains are offered at varying concentrations. One strain is more conducive to development and reproduction rates than the other, and the worms show a corresponding preference for that strain, even at concentration ratios of less than 1:16 (9). This assay is a useful way to determine the threshold between choices, or the ratio of concentrations where the worms will opt for the less nutritious but much more abundant food source. A slightly different experiment was done in which worms were isolated from their only food source by a ring of hydrophobic material (10). Hydrophobic substances are thought to signal danger to *C. elegans*, because they can cause the animals to dry out and die. Here, the animals must balance the value of food with the danger of desiccation.

Stimuli that signal danger and value often use different senses (e.g. temperature and smell) simultaneously, indicating a capacity for multisensory processing (10).

All of these assays rely on localization behavior, which is the worms' ability to move to a more favorable location. Localization uses input from a variety of senses and processes in *C. elegans*, as demonstrated above, which Faumont et al. (2012) note is consistent with their lifestyle in which "both habitat and resources are believed to be patchy, transient, and unpredictable" (1).

Weighing food abundance against risk

Several studies have investigated the behavior of *C. elegans* in the context of food danger versus nutritional value. Hilliard et al. (2004) found that *C. elegans* tends to avoid certain substances that are toxic and taste bitter to humans (6). Similarly, Zhang et al. (2005) showed that "*C. elegans* modifies its olfactory preferences after exposure to pathogenic bacteria, avoiding odours from the pathogen and increasing its attraction to odours from familiar nonpathogenic bacteria" (8). Because many plant and bacterial toxins taste bitter, such a correlated response is unsurprising, and can serve as a further probe into these decision making processes.

Four neurons within each amphid have been identified as taking a part in the aversion response, denoted ASH, ADL, ASK, and ASE (6). ASH plays the largest role, with the other neurons apparently only taking part significantly when ASH is ablated (6). Additionally, a few genes have been discovered which code for proteins that are critical to the process, including the Gα-protein ODR-3, the ion-gated channel OSM-9, and a cytoplasmic protein OSM-10 (6). The G-protein motif is a common method of signal transduction across many organisms, and could, in conjunction with other

proteins, play a direct role in the propagation of synaptic action potentials and a subsequent behavioral response.

Figure 3 is a graph of the findings of Hilliard et al. using a bitter agent known as quinine (6). Quinine is a relatively small soluble organic molecule which tastes bitter but is relatively nontoxic, enabling experimentation without the complication of harming the subjects.

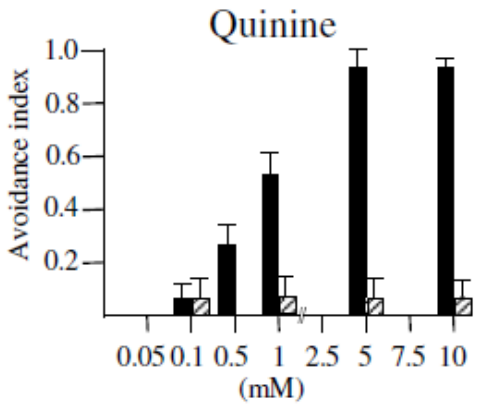

Figure 3. Avoidance index of *C. elegans* for quinine (6).

Quinine concentration was varied as indicated, with high concentrations (≥5 mM) showing little further change. Solid bars are wildtype, striped bars are qui-1 (a protein involved in quinine detection) loss-of-function mutants.

The results reported in this thesis examine the decisions of *C. elegans* when presented with food and bitterness at varying concentrations. In each experiment, animals were presented with 6 alternative food sources, comprising a menu of options (Figure 4). In the first set of experiments, several concentrations of quinine with constant amounts of food at either a high or low level were presented and the subjects' localization patterns were observed, to determine the relevant range of quinine concentrations to use in future experiments (Figure 5). The second set of experiments examined whether *C. elegans* behaved rationally—making decisions that are consistent

with maximizing the satisfaction of their preferences—by varying both quinine concentration and food abundance in a variety of 6-part gradients (Figure 5).

Figure 4. 6-arm maze on agar.

Worms are added to the area where the arms intersect, with the terminal knob on each end containing 3 µL food-quinine mixture. Red circle indicates the region in which worms are included for that arm's count.

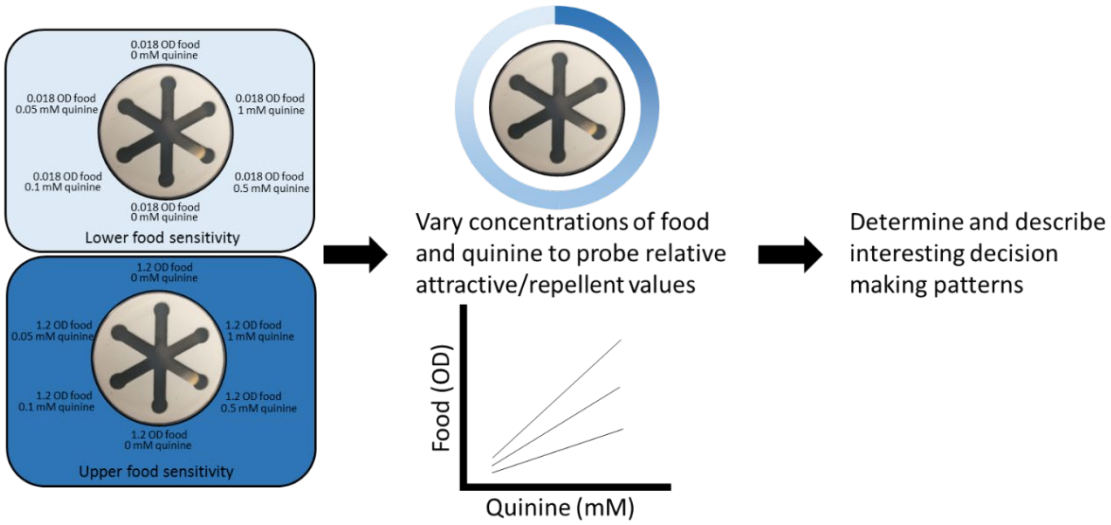

Figure 5. Schematic of experiments.

The first set of experiments determined the range of quinine concentration where *C. elegans* are sensitive at the two extremes of food concentration. The second set of experiments, in which both food and quinine concentration were varied, produced data which were evaluated for internal consistency.

Testing economic rationality

To determine whether *C. elegans* behaved rationally, the data from the second set of experiments were analyzed using an algorithm developed for studying decision making in economics in the early 20th century, and refined in 1982 by Hal R. Varian (11). The algorithm is part of a theory called the Generalized Axiom of Revealed Preference (GARP) (11). The theory posits that preferences are dictated by a utility surface, a concave set of curves (one for each menu) which can be used to predict the interaction between two goods in the preference of a subject. Because each unit increase of one good while maintaining the other brings less of a return (e.g. at some point, one more bag of chips is hardly desired), utility is maximized at some intermediate point on the curve. The relationship between choices along this continuous surface can be explored more readily with discreet bundles—particular

items on the menu[1]—with the following two definitions. First, we say that a subject directly reveals preference for bundle X over bundle Y when the subject chooses X over Y, or chooses X over Y', which is a choice with no less of either good product than Y, and more of at least one (11). Second, we say that a subject indirectly reveals preference for bundle X over bundle Y when the subject chooses X over any number of intermediates which are chosen over Y. The intermediates can be used to determine whether choices are consistent between two menus.

For instance, in menus A and B, shown in Figure 6, we know that c>a and d>b, because each is equal to the other in one good and greater in the other good. If a and b

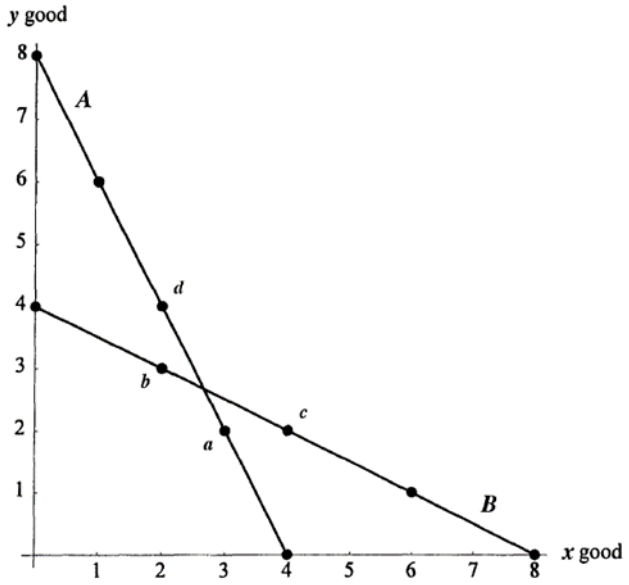

Figure 6. Revealed preference of goods x and y.

Menus A and B consist of a budget line with several bundles, shown as dots.

are chosen by the subjects, we also know that a>d and b>c. Following the string of intermediates, one can show that a>b, because a>d>b. However, one can also show that

[1] In this case, a bundle is a particular food-quinine mixture, of which there are 6 in each menu.

b>a, because b>c>a. Because the two chains of logic conflict, we say these choices are irrational. This is called a transitivity violation.

Danger versus safety

For the GARP algorithm to work, the data must present two positive alternatives, rather than a positive and a negative. In order to carry out the analysis of these experiments, which presented a menu with food (a good) and quinine (a bad), we therefore reversed the quinine axis such that quinine is decreasing and safety (a good) is increasing. Using data from Hilliard et al., unpublished work from the Lockery Lab[2], and the results from the first set of experiments, the range of food and quinine concentrations to probe were determined (6). We defined an arbitrary safety index as the maximum concentration of quinine, 2 mM, minus the concentration present in a given arm. We designed 10 equally-spaced budget lines (Figure 7). Each intersection of a pair of lines, as in Figure 6, is tested for transitivity violations using the GARP algorithm (11).

[2] Sattler & Lockery, unpublished.

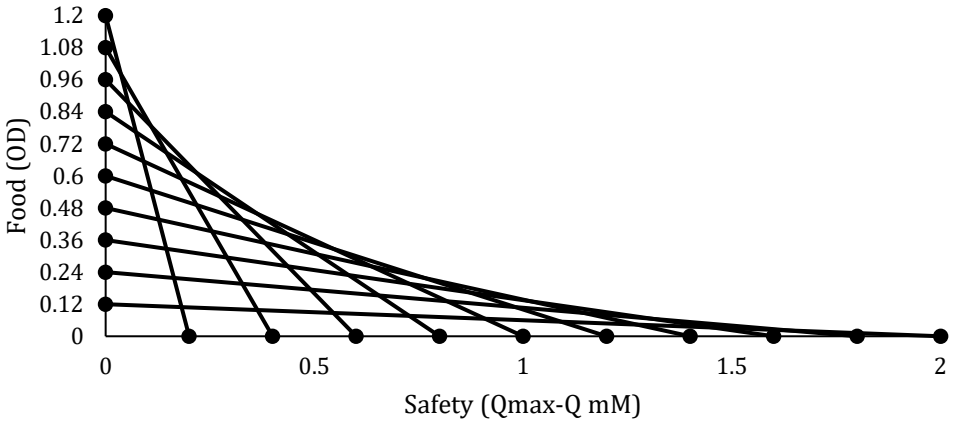

Figure 7. Budget lines for the second set of experiments.

The x-axis is defined as safety rather than [quinine] so that both axes increase in good from the origin. Each budget line represents a set of experiments with 1 menu of 6 bundles, evenly spaced along the line.

Methods

Preparation

Synchronization and cleaning of worms

N2 worms were used for all experiments. Between 20 and 30 adult worms were added to several agar plates with a small amount of OP-50 bacteria as a food source. The plates were incubated at 20°C for 8 h, during which time the worms laid several eggs each. After 8 h, the adult worms were removed from the plates, leaving about 100 eggs on every plate. These were incubated at 20°C for 72 h, the time required for development into adults. The synchronized adults were then washed with 2 mL buffer from the plates into Eppendorf tubes and centrifuged at 4000 rpm for 30 s, forming a loose pellet at the bottom. The supernatant of buffer, juvenile worms, food, and other impurities was pulled off and discarded, and 1 mL clean buffer was added to the tubes. Spinning the tubes and removing and replacing the supernatant was repeated 4-5 times to remove as much food residue as possible. The worms from all the tubes were then collected into a single class tube using a glass pipette.

Preparation of bacterial solutions

All experiments used *E. coli* OP50-1 as the food source. To prepare a stock solution of the bacteria, a container of LB broth + 1 μL/mL streptomycin was seeded with a sample from a frozen OP-50 stock and shaken at 37°C for 24 hours. The solution was refrigerated, and a fresh solution was prepared after 7-10 days.

To prepare food for an experiment, 50 mL bacterial stock was added to a 50-mL vial and centrifuged at 5000 rpm for 7 minutes. The supernatant was discarded, 10 mL

buffer was added, and the vial was agitated by vortex to resuspend the bacteria. The previous two steps were repeated for a total of 3 spins. The volume of the final solution was approximated by dividing its mass by the density of water. The optical density of the solution was determined by spectrophotometry (Laxco DSM-micro) in triplicate.

For the limit experiments, 2 dilutions were prepared: one at 0.036 OD and one at 2.4 OD. Dilutions were calculated using $M_1V_1 = M_2V_2$, the optical densities were measured in triplicate, and further adjustments were made as needed to approach the desired OD.

For the GARP experiments, 6 dilutions were prepared for each budget line, with optical densities ranging from 0 (buffer only) to 2.4 OD (Table I).

Preparation of quinine solutions

A stock solution of quinine hydrochloride dihydrate (Sigma-Aldrich 6119-47-7) in buffer was prepared using a precision balance and the molar mass (396.91 g/mol).

For the limit experiments, 5 solutions were prepared from a 2 mM stock solution, with concentrations as follows: 2 mM, 1 mM, 0.2 mM, 0.1 mM, and 0 mM (buffer only). Concentrations were calculated as previously and prepared using a volumetric pipette.

For the GARP experiments, 6 dilutions were prepared for each budget line, with concentrations ranging from 0 mM (buffer only) to 2 mM (Table I).

Preparation of mazes

Six-armed radial mazes were cut from 2 mm craft foam using a LASER running a program for the design[3].

Preparation of plates.

Each experiment required 24 plates, and 28-32 were prepared to allow for mistakes in preparation. Clean agar plates, stored in a refrigerator to control humidity, were air-heated at 117°C for 45 minutes. The heat was then turned off and the plates cooled at room temperature for at least 30 minutes.

After cooling, mazes were lightly pressed onto each plate. The solutions for each arm were prepared by combining the appropriate food and quinine solutions, and 2.5 μL was pipetted to the center of each arm end. Once all solutions were added to each of the plates, cleaned worms were pipetted to the center of the mazes (target 10-20 for the limit experiments; 30-50 for the GARP experiments).

Table I. Budget Line Bundles for GARP Experiments.

Line	Good	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 6
1	OD Food	1.20	0.96	0.72	0.48	0.24	0
	Safety	0	0.04	0.08	0.12	0.16	0.20
2	OD Food	1.08	0.86	0.65	0.43	0.22	0
	Safety	0	0.08	0.16	0.24	0.32	0.40
3	OD Food	0.96	0.77	0.58	0.38	0.19	0
	Safety	0	0.12	0.24	0.36	0.48	0.60
4	OD Food	0.84	0.67	0.50	0.34	0.17	0
	Safety	0	0.16	0.32	0.48	0.64	0.80

[3] Program by Lockery.

5	OD Food	0.72	0.58	0.43	0.29	0.14	0
	Safety	0	0.20	0.40	0.60	0.80	1.00
6	OD Food	0.60	0.48	0.36	0.24	0.12	0
	Safety	0	0.24	0.48	0.72	0.96	1.20
7	OD Food	0.48	0.38	0.29	0.19	0.10	0
	Safety	0	0.28	0.56	0.84	1.12	1.40
8	OD Food	0.36	0.29	0.22	0.14	0.07	0
	Safety	0	0.32	0.64	0.96	1.28	1.60
9	OD Food	0.24	0.19	0.14	0.10	0.05	0
	Safety	0	0.36	0.72	1.08	1.44	1.80
10	OD Food	0.12	0.10	0.07	0.05	0.02	0
	Safety	0	0.40	0.80	1.20	1.60	2.00

Experimentation

The plates were divided into two sets of 12 and placed on numbered clear plastic trays. High-definition scans of the trays were taken individually at times 0, 15, 30, 45, and 60 minutes, where t = 0 is the time of initiation of the first scan for that tray. Care was taken to minimize the time between adding the worms to the plates and the start of scans. The mazes were then removed with tweezers and a final scan was taken. Scans were taken with an Epson scanner (24 bit color, resolution 1200 dpi, unsharp high, grain reduction medium, dust removal on/off) and saved as .JPEG or .TIFF files.

The temperature was monitored by measuring the temperature of two plates on each tray before and after the scans, to ensure the plates did not exceed 23°C.

Analysis

The proportion of worms p_i in a given food source i is defined as

$$p_i = \frac{n_{arm,i}}{n_{tot}} \quad (1)$$

where $n_{arm,i}$ is the number of worms with at least a portion of their body within the terminus of arm i, and n_{tot} is the sum of worms either anywhere in the maze for the limit experiments, or in any arm terminus for the GARP experiments (Figure 4). The proportions were determined for each arm of each plates at time points t = 45 and 60 and averaged. For the GARP experiment's calculations, data from plates with either fewer than 10 worms within the maze at either time point or the number of worms in all arm termini (n_{tot}) equal to 0, were discarded.

For statistical analysis, n was determined as the number of plates. The number of worms on a plate had no impact: all plates were weighted equally.

The number of transitivity violations was determined using an algorithm which was modified from Varian (1995) (11). In the future, this will be referred to as the GARP algorithm.

Results

Food concentration impacts threshold of aversion to toxicity

To determine a range of quinine concentration across which *C. elegans* is sensitive, worms were placed on a radial maze with 6 food sources with constant OD food and modulated quinine concentration. One set (Fig. 8a, c) was conducted with food at 1.8 x 10^{-2} OD, and the other set (Fig. 8b,c) was conducted with food at OD 1.2, the lower and upper limits, respectively.

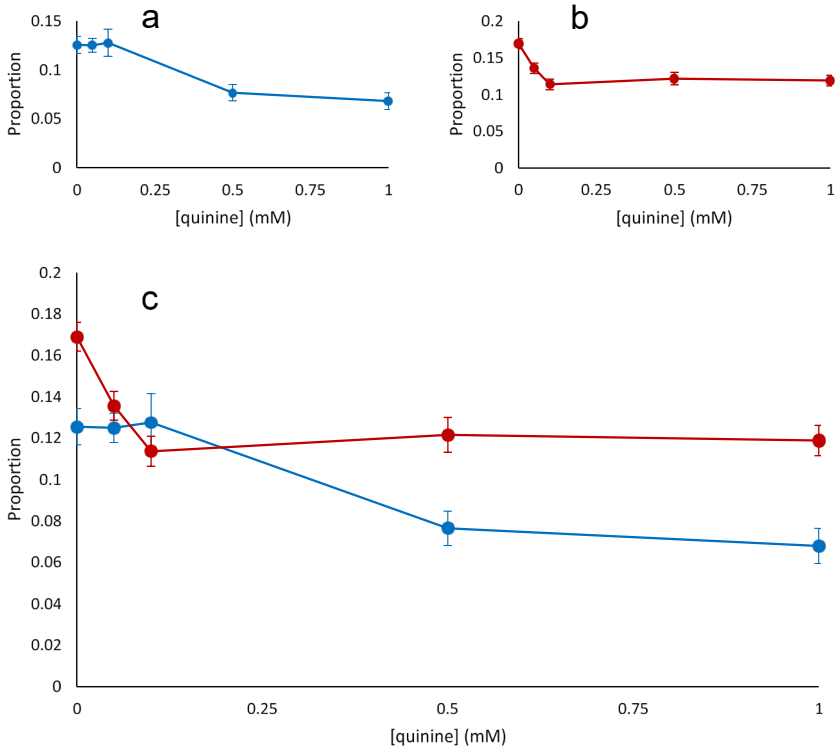

Figure 8. Threshold for aversion to quinine depends on food concentration.

Average proportions of worms at a,c) lower-limit (1.8 x 10^{-2} OD) and b,c) upper-limit (1.2 OD) food concentrations versus quinine concentration. Error bars: mean ± SEM, $66 \geq n \geq 144$.

Figure 8c reveals no significant difference in preference for low-concentration food sources across 0 to 0.1 mM quinine, a sharp decrease between 0.1 mM and 0.5 mM, and once again no significant change in preference between 0.5 mM and 1 mM quinine. In contrast, with high-concentration food sources, preference decreases steadily from 0 mM to 0.1 mM quinine before remaining approximately constant through 1 mM. This difference suggests that either sensitivity of detection, or amplitude of chemotactic response, to toxicity is dependent on the quality of the food sources available: less concentrated food sources result in a higher tolerance of environmental quinine than highly concentrated food.

There is also a significant decrease in the total proportion of animals making a choice, Σp_i, when the food is at a lower concentration, as indicated by the lower proportions at almost every concentration (Figure 8c).

C. elegans exhibits rational behavior in food-safety assay

Choice for each budget line was determined qualitatively by inspecting plots of the proportion of worms in each food source, and selecting the arm containing the highest average proportion of animals (Figure 9). In some cases, more than one contiguous arm was equivalently populated, and their values were therefore averaged to give a single choice. To determine rationality, the number of transitivity violations among these choices was found. The choices for lines 1, 7, and 10 (see Table I) were not included, because the choice in these lines was on the edge—that is, it had more of one of the goods than any other option available on the menu (Arms 1 and 6)—and the GARP algorithm can only be performed on data in which the choices were internal. The values of both goods for each of the 7 lines' choices were input into the GARP

algorithm. The analysis found no transitivity violations, indicating a high degree of rationality.

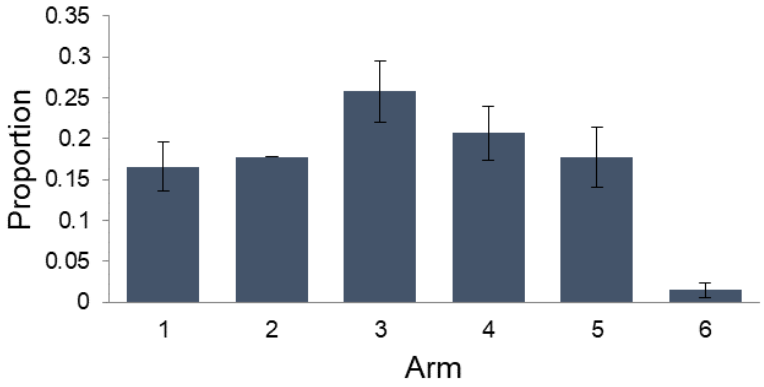

Figure 9. Representative budget line proportions by arm (Line 5).

Proportions at each arm suggest, in this case, a preference for the bundle in Arm 3 (0.432 OD food, 0.4 safety, Table I). For each budget line, food decreases and safety increases from Arm 1 – Arm 6. Error bars: Mean ± SEM, $13 \geq n \geq 23$.

Discussion

In the environment, *C. elegans* is exposed to numerous food sources, varying in concentration, nutritional value, safety, and other characteristics (8). Because of the variation, *C. elegans* must have pathways in place to perform higher-level decision making, weighing information on as many characteristics as possible to maximize satisfaction and, ultimately, survival and reproduction. In light of the natural exposure to variation, a modulated response is therefore to be expected.

In the case of the limit experiments, where food concentration was held constant while varying quinine concentration, one possible response might have been that subjects tolerated more danger when food was highly concentrated—making each swallow of food highly nutritious, and therefore worth greater risk. However, we found the threshold aversion to quinine was modulated such that the subjects tolerated more danger when food was scarce. This striking result suggests that the weighting of food and safety by the *C. elegans* nervous system favors food—required for survival and procreation—over safety—which would reduce the gradual build-up of toxin and eventual death.

To determine rationality, several budget lines with a wide variation of food concentration and safety were tested, and transitivity violations were counted. Because a transitivity violation indicates an internal inconsistency, a larger number of transitivity violations points to less rationality in a subject. In these experiments, no transitivity violations were found, suggesting that the decision-making pathways of *C. elegans* are highly tuned for such situations. Humans, by contrast, often make sets of decisions which contain a few transitivity violations (11), even in assays of comparable

simplicity. Perhaps the difference is due to humans' remarkable tendency to value non-utilitarian characteristics, sometimes making decisions based entirely on trivial features, through higher-order processing not available in *C. elegans*.

These results suggest that *C. elegans* contains a highly dynamic decision making network, which can respond differently depending on the specific situation. While sophisticated, this network is nonetheless consistent across a wide range of food and quinine concentrations. For this reason, future work in the neurology of *C. elegans* is promising. While different from the human nervous system in obvious ways, there is nevertheless a high degree of complexity, allowing for considerable discovery. Furthermore, the relatively high homology between humans and *C. elegans* at the level of receptors and gene function gives further relevance to study in this organism.

This study tested value-based decision making exclusively on the behavioral level. Future work investigating the activity of the amphid neurons—particularly ASH, ADL, ASK, and ASE—and eventually the manner through which the input from the different senses interact on the molecular level, will couple with these results to bring us closer to the solutions to many unanswered questions about the nervous system.

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